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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,920	12/21/2000	Kenneth C. Parker	SY9-155 RCE	2871

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EXAMINER	
SKIBINSKY, ANNA	
ART UNIT	**PAPER NUMBER**
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/745,920	PARKER, KENNETH C.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-24 and 26-33* is/are pending in the application.

4a) Of the above claim(s) *30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-24 and 26-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/05/2007 has been entered.

Applicant's amendments to claim 23 are acknowledged. Claims 1-7, 9-24, 26-29 are under examination.

Election/Restriction

Claims 30-33 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/24/2002.

Claim Rejections - 35 USC § 112-2nd paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-7, 9-24, 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 1 recites the limitation "said **biological** fragment detection parameter" in line 13. There is insufficient antecedent basis for this limitation in the claim. For the purpose of examination, this will be interpreted as "said biomolecule fragment detection parameter" for which there is antecedent basis in line 12.

4. Claim 1 recites the limitation "said **biological** fragment" in line 17. There is insufficient antecedent basis for this limitation in the claim. For the purpose of examination, this will be interpreted as "said biomolecule fragment" for which there is antecedent basis in line 4.

5. Claim 23 recites "the step for determining the **biological** fragment score comprises" in lines 9-10. There is insufficient antecedent basis for this limitation in the claim. For the purpose of examination, this will be interpreted as "the step for determining the biomolecule fragment score comprises" for which there is antecedent basis in line 9.

6. Claim 23 recites the limitation "said **biological** fragment detection parameter" in lines 15-16. There is insufficient antecedent basis for this limitation in the claim. For the purpose of examination, this will be interpreted as "said biomolecule fragment detection parameter" for which there is antecedent basis in line 14.

7. Claim 23 recites "determining a detection likelihood for said mass signal which defines a biomolecule fragment detection parameter," (claim 23, lines 12-13) and then that "a biomolecule fragment detection parameter ... comprises a numerical value that is a measure of the likelihood of detecting the biomolecule fragment" (claim 23, lines 16-17). It is not clear how the likelihood can define a biomolecule fragment detection

parameter while the a biomolecule fragment detection parameter comprises the likelihood. The limitation appears to be circular and clarification is requested. For the purpose of examination, the biomolecule fragment detection parameter is interpreted as being the same as in claim 1.

8. Claim 23 recites "determining said biomolecule fragment score from said mass signal intensity, said biomolecule fragment detection parameter, and said mass error for said mass signal", (lines 25-27). It is unclear how this limitation relates to the "determining said biomolecule fragment score" recited in lines 9-10. The steps for "determining said biomolecule fragment score" are recited in lines 12-24 so it is unclear if the second "determining said biomolecule fragment score" (lines 25-27) is an additional step which recites the use of the mass signal intensity, mass error and mass signal or if this is a recitation of another "biomolecule fragment score" that is to be determined.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yates, III et al. (P/N 6,017,693) in view of Gras et al. (Electrophoresis, 1999 vol. 20, pages 3535-3550) in view of Wright et al. (P/N 5,710,713).

The instant claims recite a method of determining a likelihood of the presence of a biomolecule in a sample comprising determining a biomolecule fragment score for a signal wherein the biomolecule fragment score comprises a biomolecule fragment detection parameter comprising a measure of the likelihood of detecting the biomolecule fragment and mass error for the mass signal wherein the mass error is the difference between the mass corresponding to the mass signal and a mass of the biomolecule fragment.

Yates, III et al. describe a method of using tandem mass spectrometry to determine sequences that are likely to be identical to an experimentally derived peptide (col. 2, lines 22-27). Yates, III et al. describe introducing an unknown peptide into a first mass spectrometer to separate it from the rest of the sample (col. 2, lines 54-64). The peptide and its fragments are then passed through a second mass spectrometer to obtain an intensity and mass-to-charge ratio (m/z) (col. 3, lines 4-7), which includes

measuring mass signals and a mass spectrum of a biomolecule fragment as seen in Figure 5 (col. 3, lines 7-9). Yates, III et al. describe a method in Figure 2 where an unknown (12) is analyzed in a tandem mass spectrometer (14) to obtain fragment spectrum (16) and compared (24) to the mass spectra (22) of proteins from a protein sequence library (20) on a computer. Yates, III et al. describe performing this comparison and calculating a closeness-of-fit measure or score for each of a plurality of mass spectra (col. 4, lines 9- 16). Yates, III et al. describe determining if a fragment mass is found in a measured fragment spectrum and scores are generated and sorted in a repeated cycle which results in one or more candidate amino acid sequences (col. 3, lines 21-28). Yates, III et al. describe high-scoring candidate sequences (col. 3, lines 29-30). Yates, III et al. describe a mass tolerance of the unknown peptide from which spectra from known sequences (i.e. potential source biomolecules) are identified if they fall within this tolerance amount (col. 4, lines 59-67 and Figure 4) which is reasonably interpreted as the biomolecule fragment detection parameter. Yates, III et al. describe an example using a tolerance of +0.05% of the mass of the unknown peptide used (col. 5, lines 25-26) which is reasonably interpreted as a detection efficiency as stated in claims 7 and 24. Yates, III et al. describe the high probability or likelihood that the unknown peptide has an identical amino acid sequence to one of the subsequences taken from the protein sequence library due to the high closeness-of-fit score with respect to the spectra comparison (col. 4, lines 16-23). Yates, III et al. further describe the high probability of the unknown protein and the known protein from the library as being identical or similar with subsequences with high closeness-of-fit scores (col. 4,

lines 23-29). Yates, III et al. describe performing further MS-MS analysis if original scoring procedures do not delineate an answer of protein match (col. 8, lines 53-61) as stated in claim 23. Yates, III et al. describe the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62). Yates, III et al. describe normalizing the spectrum (col. 4, lines 35-38) which is reasonably interpreted as a form of calibration as in instant claim 4. Yates, III et al. describe the above-mentioned procedure as being performed automatically on a computer (col. 4, lines 30-34). Yates, III et al. describe computational resources and storage facilities (col. 9, lines 24-49 and col. 21, lines 8-10) as stated in claims 28 and 29. Yates, III et al. describe identifying 200 of the most intense ions from the experimentally-derived fragment spectrum (col. 4, lines 44-45) as mentioned in claim 14. Yates, III et al. describe the calculation of closeness-of-fit (56) in Figure 3 and then the selection of sequences with the highest scores (58). Yates, III et al. describe outputting matching data for sequences with the highest correlation function (62) which suggests that any scores lower than the highest scores are likely absent and therefore are not outputted (also see Figure 6D) as stated in claim 2. Yates, III et al. do not teach correcting a mass intensity for an isotopic variant (claim 3), removing noise (claim 5), removing artificial background intensity (claim 6), weighted biomolecule scores, fragment counts, and signal intensity scores to determine the likelihood of the presence or absence of a biomolecule as well as determining a relative concentration based on the biomolecule score.

Yates, III et al. describe a method of using tandem mass spectrometry to match experimentally determined sequences to protein sequences in a sequence library on a computer. Yates, III et al. does not however teach the use of mass intensity scores (as pointed out in the Office Action of April 22, 2005, page 5, line 13). Yates does not teach a "biomolecule fragment detection parameter."

Gras et al. teaches the calculation of an "identification score" on page 3542, Section 2.4.3, The algorithm (lines 5-6 of section), and defines the parameters for the scoring function in Section 2.4.3.2, Definition of the score, (lines 21-27 of section and equation). This was pointed to on page 6, lines 11-13 in the Office Action of April 22, 2005.

The limitation in claim 1 recites that the biomolecule fragment score comprises a function of a biomolecule fragment detection parameterwhich is the "likelihood of detecting said biomolecule fragment ... based at least in part on relative mass signal intensity relationships." Gras et al. also uses, in part, the intensity of the peaks to determine a score for matching the searched protein and the candidate proteins through peptide mass fingerprinting.

Furthermore, as required by claim 1 which recites "mass error", Gras et al. teach a "mass level" on page 3541, column 2, paragraph 3 which corresponds to the mass error of the mass signal as recited in claim 1. The degree of matching between the mass of the peptide fragment and the mass of the searched protein is characterized. The mass level (page 3541, column 2, paragraph 4) includes determining the confidence level for the match based on comparing the experimental mass with the

theoretical mass of the protein. These "level 2" mass parameters are further described (page 3543, column 1, paragraph 4 to column 1, lines 1-2) to include the standard deviation that gives insight to the correspondence between the masses of the matched peptides and the spectrometer error.

Gras et al. describe a program that identifies a protein based on mass spectra despite chemical modifications (abstract, lines 1-5) which could be an isotopic variant as stated in claim 3. Gras et al. also describe this determination of isotopic variants via software that often comes with the spectrometer (page 3538, col. 1, lines 1-5 and col. 1, third paragraph). Gras et al. describe a trend or baseline as the signal produced if no material entered the mass spectrometer and in the absence of noise (page 3537, col. 2, lines 10-14; page 3538, col. 1, lines 18-24; and Figure 1) which is reasonably interpreted as the removal of noise and background intensity as stated in claims 5 and 6. Gras et al. describe the smoothing out of error functions related to the mass signals (page 3538, lines 21-26). Gras et al. describe using selected parameters to search proteins in a database that match the experimental spectra and assigning a score to the candidate protein (page 3541, col. 1, paragraph 2). Gras et al. describe the parameters' effects on the quality and efficiency of the identification (page 3541, col. 1, paragraph 3) as mentioned in claims 7 and 24. Gras et al. describe parameters that include the maximum distance between experimental and theoretical masses, the minimum number (or score) of matched peptides necessary for a protein to be selected, and the number of peaks returned by the peak detection program (page 3541, col. 1, paragraph 4). Gras et al. describe eliminating the least likely proteins in the list of candidates using

parameters such as the minimum number of matched peptides or number of detected peaks, as well as depending on their thresholds (page 3541, col. 2, paragraph 1). Gras et al. describe the parameter of peak intensity in the mass spectrum as well (page 3542, col. 2, lines 40-44). Gras et al. describe a mass level parameter that characterizes the degree of match between the experimental mass and the peptide mass of the search library protein (page 3541, col. 1, paragraph 3) that is reasonably interpreted as a mass error. Gras et al. describe defining score calculations by determining the most important parameters, their relative weights and how to integrate them all into the score calculation (page 3542, col. 2, lines 20-23). Gras et al. describe counting the number of experimental masses matching theoretical peptide masses (page 3542, col. 2, lines 29-33) which are fragment counts. Gras et al. describe the concept of the more identified masses a protein has in the mass spectrum, the higher is the confidence for its identification (page 3542, col. 2, lines 33-35). Gras et al. describe assigning weights to each peptide mass, depending on the presence of a match resulting in a score calculation (page 3542, col. 2, lines 36-41 and page 3543, col. 2, lines 15-19). Gras et al. describe taking into account the calibration error of the measuring device, eliminating masses that are too far from the regression line, and repeating this process when the previous masses were eliminated in the previous step (page 3543, col. 1, paragraph 3). Gras et al. describe identifying proteins via scores obtained of the proteins in a ranked list of candidate proteins (page 3543, col. 2, lines 37-41).

Wright et al. describe measurement of concentration in the mass spectrometer, its use in standardization of the process including relative estimates, and relative errors resulting without a calibration correction (col. 17, lines 6-26) as stated in claim 16.

Yates, III et al. state that interpretation of the fragment spectra to produce candidate amino acid sequences is time-consuming, often inaccurate, and highly technical (col. 1, lines 52-59). Yates, III et al. note that relying on human interpretation often means that analysis is relatively slow and lacks strict objectivity (col. 1, lines 59-60). They further state that approaches based on peptide mass mapping are limited to peptide masses derived from an intact homogeneous protein generated by specific and known proteolytic cleavage (col. 1, lines 61-64). Yates, III et al. state that it would be useful to provide a system for correlating fragment spectra with known protein sequences in a fast and objective way (col. 1, lines 65-67). Yates, III et al. show a spectral interpreting method that could be used with any size peptide (col. 20, lines 59-60). However, Yates, III et al. note that certain variations and modifications could be made to their method of identification of spectral data (Yates, III et al., col. 2, lines 5-27) in order to provide more accurate results (Yates, III et al., col. 1, lines 52-59). Yates III et al does not teach the likelihood of the presence or absence of a biomolecule or determining a relative concentration based on the biomolecule score.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include features such as correcting a mass intensity for an isotopic variant, removing noise and artificial background intensity, creating weighted biomolecule scores, fragment counts, and signal intensity scores to determine

the likelihood of the presence or absence of a biomolecule, as stated by Gras et al., as well as determining a relative concentration based on the biomolecule score, as stated by Wright et al., to the method of Yates III et al. where the motivation would have been to provide precise and fast determination of peptide masses, even if the peaks are of low intensity and overlap (Gras et al., abstract, lines 6-7) and to provide accurate and precise concentration estimates (Wright et al., col. 17, lines 19-21) to create more accurate results in mass spectral identification, as stated by Yates, III et al. (col. 1, lines 52-59). Thus, Yates, III et al., in view of Gras et al. in view of Wright et al. make obvious the limitations of claims 1-7, 9-24, and 26-29.

REPLY TO ARGUMENTS

11. Applicant's arguments filed 3/5/2007 have been fully considered but they are not persuasive.

Applicants argue that the Final Office action 3/05/07 fails to show where the cited reference teaches a "biomolecule fragment detection parameter" wherein the "biomolecule fragment detection parameter" [takes] into account the likelihood of detecting a biomolecule fragment as a mass signal in the mass spectrum of the sample (Remarks, page 16, lines 1-27). Applicants further argue (page 16, lines 3-10 from bottom and page 17, lines 19-22) that the "[biological fragment detection] parameters reflect the general relative mass signal intensity relationships between biomolecule fragments," and the general relative mass signal intensity relationships that arises from

the differences in the likelihood of detecting different biomolecule fragments as a mass signal in the mass spectrum of the sample.

In response, it is noted that Gras et al. use the intensity of the peaks (i.e. mass signal in the mass spectrum of the sample) to determine a score for matching the searched protein and the candidate proteins through peptide mass fingerprinting. The argued limitation is met by Gras et al. who teach the calculation of an "identification score" (page 3542, Section 2.4.3, The algorithm (lines 5-6 of section)), and define the parameters used in the scoring function (Section 2.4.3.2, "Definition of the score," lines 21-27 of section and equation). Furthermore, Gras et al. teach a "maximum likelihood" which relies on the probability of finding a mass in the mass distribution of peptides (pages 3539 to 3540, connecting paragraph). Additionally, Yates, III et al. describe the high probability or likelihood that the unknown peptide has an identical amino acid sequence to one of the subsequences taken from the protein sequence library due to the high closeness-of-fit score with respect to the spectra comparison (col. 4, lines 16-23).

12. Applicants argue (Remarks, page 18, lines 1-8, lines 21-23 and page 19, lines 1-8) that Gras et al. fails to show "the likelihood of detecting said biological fragment being based at least in part on relative mass signal intensity relationships between biomolecule fragments, fractions of biomolecule fragments, or both" for a biomolecule fragment.

13. In response, Gras et al. also teaches a maximum likelihood which depends on the probability of finding a mass (page 3540, lines 1-14). Gras et al. also uses, in part,

the intensity of the peaks to determine a score for matching the searched protein and the candidate proteins through peptide mass fingerprinting (page 3540, col. 1, line s17-29) which reads on the instant limitation because the spectrum used includes mass signal intensities which belong to related peptide fragments.

Applicants state that they do not understand the statements in the Final Action at pages 3-4 with respect to "mass level" (Remarks, page 19, lines 16-25)

In response, said statement in the Final Office action was intended to address that Gras et al. teach the limitation of "mass error" as required by claim 1. Gras et al. teach a "mass level" (as pointed out in the Office Action of April 22, 2005, page 5, lines 13-15) on page 3541, column 2, paragraph 3 which corresponds to the mass error of the mass signal.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SUPERVISORY PATENT EXAMINER